IB/04/03378

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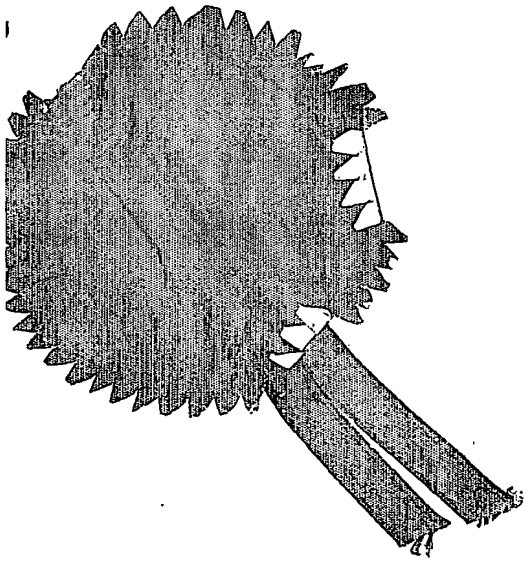
INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Provisional Specification*** *filed in connection with Application for Patent No.* ***1285/Del/2003*** *dated* ***17th October 2003***.

Witness my hand this 1st day of March 2005.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1 1285 DEL 03

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"ORAL MATRIX FORMULATIONS OF DOXAZOSIN"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. GIRISH KUMAR JAIN
b. ANANT RAMESH KETKAR
c. ASHOK RAMPAL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10

Following declaration was given by the inventors or applicants in the convention country:

We, GIRISH KUMAR JAIN, ANANT RAMESH KETKAR, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (GIRISH KUMAR JAIN)

b. (ANANT RAMESH KETKAR)

c. (ASHOK RAMPAL)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Provisional Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.**3,000**/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **13TH** day of **October, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

(See Section 10)

ORAL MATRIX FORMULATIONS OF DOXAZOSIN

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Field of invention:

The present invention relates to the matrix formulation for extended release of doxazosin mesylate, comprising doxazosin or its salt, solvate, hydrates, enantiomer or mixtures thereof, at least one release retarding ingredient and other pharmaceutically acceptable excipient.

Background of the invention:

Doxazosin, 1-(4-amino-6, 7-dimethoxy -2-quinazolinyl)-4-[(2,3-dihydro-1, 4-benzodioxin-2-yl)-carbonyl]-piperazine monomethanesulfonate and its pharmaceutically acceptable acid addition salts are described in US 4188390. Doxazosin is a quinazoline derivative that acts through selective inhibition of alpha-1 adrenoceptors and is indicated in hypertension, either alone or in combination with other antihypertensive agents and for the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia.

Doxazosin is well absorbed after oral administration with bioavailability of 65% and a mean plasma half-life of about 11hrs.

In clinical practice for treatment of hypertension and symptoms of benign prostatic hyperplasia (BPH), doxazosin therapy is initiated at 1 mg standard immediate release dosage form per day and the dose is doubled every 7-14 days to a maximum recommended dose of 16 mg per day for hypertension and 8 mg per day for benign prostatic hyperplasia (BPH) till the blood pressure or urinary flow rate or BPH symptoms are controlled. This regimen can require up to three to four titration steps to achieve therapeutically effective doses in a manner likely to avoid first dose side effects. This can be achieved by developing a formulation with significantly gradual absorption of doxazosin with prolonged Tmax and reduced peak to trough blood level fluctuation of doxazosin compared to standard immediate release dosage form available.

The above problem was solved by the development of Cardura-XL osmotic dosage form by Pfizer. The Cardura-XL formulation uses osmotic system to deliver doxazosin for extended period of at least about 24 hours. The advantages of such system are that the release of the drug is pH independent and gastrointestinal motility does not significantly affect the rate of release of the active ingredient from such dosage form. The active ingredient is released from said osmotic dosage form in zero order thus controlling active ingredient delivery rate. However, development of such a system requires more sophisticated facilities for eg. laser drill and require

especially skilled persons to manufacture the dosage form. Such special requirements in tern have implications on overall production cost and time of production compared to conventional matrix or other tablet dosage form.

The matrix formulations of the present invention are relatively easy to manufacture, do not require especially skilled persons and manufacturing operations and are relatively simple and cost effective. The matrix formulations of the present invention releases the drug over extended period of time from about 12 hours to about 24 hours such that there is substantially gradual absorption of doxazosin with prolonged T_{max} with reduced peak to trough doxazosin blood level fluctuation, thereby enhancing the pharmacokinetic profile and affording simplified dosing schedule. Thus the formulations of the present invention may be administered at higher initial daily dose (4 mg per day) than doxazosin standard 1 mg, while avoiding significant first pass side effect. Thus the therapeutic effective levels of doxazosin can be reached more rapidly without excessive plasma levels and more uniform plasma concentration may be provided with minimal peak to trough blood level fluctuation.

EP700285 patent discloses drug delivery compositions of alpha adrenoreceptor blocking agents with a biphasic drug release profile. The said patent teaches matrix compositions using hydroxypropyl methylcellulose and further coating dissolved by conditions present in the colonic region.

US4259314 patent discloses a dry pharmaceutical formulation containing a therapeutic agent and a dry carrier comprising hydroxypropyl methylcellulose and hydroxypropyl cellulose. The teachings are therein are directed towards the use of formulations with hygroscopic active ingredients.

EP862437 patent discloses a controlled-release pharmaceutical formulation for oral administration consisting essentially of: an active drug compound; low molecular weight polyethylene oxide; hydroxypropylmethyl cellulose; tabletting excipients; and optionally one or more enteric polymers

The EP0413061 teaches the sustained formulations containing active ingredient and combination of hydroxypropyl methylcellulose and hydroxypropyl cellulose. The hydroxypropyl methylcellulose used therein is selected from two different number average molecular weight of

from 30,000 to 350,000; and 9,000 to 30,000. The said patent teaches use of combination of at least three cellulose based formulations.

The US6083532 teaches the sustained release formulations comprising at least three different types of polymers including a pH dependent gelling polymer, a pH independent gelling polymer and an enteric polymer, wherein said pH dependent gelling polymer comprises at least one of an alginate, a carboxyvinyl polymer, or a salt of a carboxymethyl cellulose.

Summary of the invention:

The matrix formulations of the present invention, when ingested orally, releases the drug over extended period of time from about 12 hours to about 24 hours such that there is substantially gradual absorption of doxazosin with prolonged T_{max} and reduced peak to trough doxazosin blood level fluctuation, thereby enhancing the pharmacokinetic profile and affording simplified dosing schedule.

The matrix formulations of the present invention thus provide enhanced pharmacokinetic profile and simplify the titration schedule, permitting an initial dose of 4 mg once daily, compared with standard doxazosin, which is initiated at 1 mg per day and titrate to higher therapeutically effective dose.

In one embodiment the doxazosin matrix formulations are disclosed such that, when ingested orally, said matrix formulation provides substantially reduced C_{max} and prolonged T_{max} compared to standard immediate release dosage form containing similar amount of doxazosin to that of said matrix formulation. The matrix formulations thus show reduced peak to trough blood concentration of doxazosin and provides significantly constant doxazosin plasma concentration at steady state. The said matrix formulation may have AUC substantially lower than the corresponding standard immediate release dosage form.

In another embodiment the doxazosin matrix formulations are disclosed such that, when ingested orally, said matrix formulation induces substantially similar minimum concentration of doxazosin (C_{min}) and reduced peak to trough blood concentration of doxazosin compared to standard immediate release doxazosin dosage form containing similar amount of doxazosin to that of said matrix formulation. The said matrix formulation may have AUC substantially lower than the corresponding standard immediate release dosage form.

In still another embodiment, the doxazosin matrix formulation provides substantially similar pharmacokinetic profile compared to Cardura-XL formulation of comparative strength. Thus said matrix formulations may be bioeqivalent to the respective Cardura-XL formulation.

Detailed description of the invention:

The active ingredient as used herein refers to doxazosin or its salt, solvate, hydrates, enantiomer or mixtures thereof.

The "release retarding ingredient" as used herein and in the appended claims refers to any suitable polymer capable of retarding the release of active ingredient for about 24 hours.

The "solubility enhancer" as used herein and in the appended claims refers to any suitable agent that is capable of improving the solubility of the active ingredient.

"C_{max}" as used herein, means maximum plasma concentration of doxazosin, produced by the ingestion of the composition of the invention or the innovator reference product.

"T_{max}" as used herein, means time to the maximum observed plasma concentration.

"AUC" as used herein, means area under the plasma concentration-time curve, over specified time interval for all the compositions.

The term "bioequivalent to Cardura containing doxazosin" as used in this specification and appended claims refers to achieving a ratio (composition of the present invention/innovator product Cardura) of C_{max} and $AUC_{0\text{-}inf}$ in the range of 80 to 125%.

The amount of release retarding ingredient in the formulation varies from 10% to 70% preferably from 20 to 35%.

The release retarding ingredient may be selected from cellulose derivatives, acrylic acid or methacrylate polymers/copolymers, gums, vinyl alcohol or vinylpyrrolidone based polymers, block copolymers, polyethylene oxide or such like. The cellulose polymers are selected

hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, hydroxyethylcellulose, carboxymethylcellulose, and methylcellulose

Generally the cellulose polymers in the present formulation are hydroxypropyl methylcellulose 2208 of different viscosity grades. These polymers are categorized as low viscosity polymers having viscosity between 5 to100cps and high viscosity polymers high viscosity polymers having viscosity between 101 to 150,000cps or grater than 150,000cps.

The preferred low viscosity polymers are available from Dow Chemical Co under the brand names Methocel E-5 and Methocel K100LVCR and high viscosity polymers under the brand names Methocel K-4MCR, Methocel K 15 M CR, Methocel K100MCR.

Generally the formulation of doxazosin may comprise 5 to 40% of low viscosity hydroxypropyl methylcellulose, preferably from 8 to 25% and 5 to 40% of high viscosity hydroxypropyl methylcellulose, preferably from 8 to 20%

The gums are selected from xanthan gum, caraya gum, locust bean gum, sodium alginate, alginic acid and such like. The composition of doxazosin may comprise 1-20% of sodium alginate and alginic acid, preferably from 2-10%.

The acrylic acid or methacrylic/methacrylate based polymers may be selected from Eudragits, like Eudragit L-100, L30 D-55, L-100 55, and S-100, EPO. The composition may comprise 5 to 20% of Eudragit EPO, preferably from 6 to 10%.

The solubility enhancers may be selected from polyethylene glycols, surfactants, propylene glycol and glycerol; mono-alcohols, such as ethanol, propanol, and higher alcohols; DMSO; dimethylformamide; N, N-dimethylacetamide; 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted-alkyl-azacycloalkyl- -2-ones. The preferred solubility enhancer is 2-20% of polyethylene glycol, preferably from 5-10%.

The 'pharmaceutical acceptable excipients' may be selected from binders, diluents and lubricant/glidant.

The binders are selected from polyvinyl pyrrolidone, pregelatinized starch and gelatin, gums, microcrystalline cellulose. The preferred binder is 10 to 50% of Avicel PH 102, preferably from 20 to 40%

The diluents are selected from lactose, mannitol and microcrystalline cellulose. The preferred diluent is 15 to 50% of Lactose DCL, preferably from 20 to 40%

The lubricants/glidants are selected from magnesium stearate, zinc stearate, talc and colloidal silicon dioxide. The preferred lubricant/glidant are 0.1 to 3% of magnesium stearate, 0.1 to 2% of talc and 0.1 to 3% of colloidal silicon dioxide.

In one embodiment, the oral matrix formulation of doxazosin or its salt, solvate, hydrates, enantiomers or mixtures thereof, at least one release retarding ingredient, solubility enhancer and at least one pharmaceutical acceptable excipient.

In yet another embodiment, the oral matrix formulation of doxazosin or its salt, solvate hydrates, enantiomers or mixtures thereof, 5-40% of hydroxypropylmethyl cellulose of high viscosity, 5-40% of hydroxypropyl methylcellulose of low viscosity, 2-20% of polyethylene glycol, 15 to 50% of lactose, 10 to 50% of microcrystalline cellulose, 0.1 to 3% of magnesium stearate, 0.1 to 2% of talc and 0.1 to 3% of colloidal silicon dioxide.

In yet another embodiment, the oral matrix formulation of doxazosin or its salt, solvate hydrates, enantiomers or mixtures thereof, 8-20% of hydroxypropylmethyl cellulose of high viscosity, 8-25% of hydroxypropyl methylcellulose of low viscosity, 5-10% of polyethylene glycol, 20 to 40% of lactose. 20 to 40% of microcrystalline cellulose, 0.1 to 3% of magnesium stearate, 0.1 to 2% of talc and 0.1 to 3% of colloidal silicon dioxide

In another embodiment, the oral matrix composition of doxazosin or its salt, solvate hydrates, enantiomers or mixtures thereof are may comprise 5 to 40% of hydroxypropyl methylcellulose of high viscosity, 5 to 40% of hydroxypropyl methylcellulose of low viscosity, 1-20% of sodium alginate and alginic acid and 5-20% of Eudragit EPO, 0.1 to 3% of magnesium stearate, 0.1 to 2% of talc and 0.1 to 3% of colloidal silicon dioxide

In another embodiment, the oral matrix composition of doxazosin or its salt, solvate hydrates, enantiomers or mixtures thereof are may comprise 8 to 20% of hydroxypropyl methylcellulose

of high viscosity, 10 to 25% of hydroxypropyl methylcellulose of low viscosity, 2-10% of sodium alginate and alginic acid and 6-10% of Eudragit EPO, 0.1 to 3% of magnesium stearate, 0.1 to 2% of talc and 0.1 to 3% of colloidal silicon dioxide

In another embodiment, the oral matrix formulation of doxazosin or its salt, solvate hydrates, enantiomers or mixtures thereof, at least one release retarding ingredient, and at least one pharmaceutical acceptable excipient.

The sustained release composition may be in the form of tablets, capsules, pellets, granules or other dosage forms suitable for oral administration. The tablets may be prepared by techniques like direct compression, wet granulation or dry granulation. The tablets may be optionally coated with a non functional coating. The tablet/ minitablets may be optionally filled into capsules

The following non-limiting examples illustrate the process for making the sustained release composition disclosed in various embodiments of the specification.

Example 1

S.No	Ingredients	%
1	Doxazosin Mesylate	3.42
2	Polyethylene glycol	8.77
3	Lactose	45.61
4	Microcrystalline cellulose	22.87
5	Methocel K100MCR	8.77
6	Methocel K100LVCR	8.77
7	Mg. Stearate	0.701
8	Talc	0.701
9	Colloidal silicon dioxide	0.35

Process: -

Step 1: PEG melted on water bath and Doxazosin added to it and cooled with mixing. The cooled material is passed thru BSS # 44.

All other excipients were sifted through British Standard Sieve 44#.

Step 2: Methocel K100MCR, Methocel K100LVCR & Lactose were mixed in double cone blender for 20 minutes to obtain a blend

Step 3: The granules of Polyethylene glycol & Doxazosin Mesylate & Microcrystalline cellulose were mixed in double cone blender for 20 minutes to obtain a blend. Both the blends of step 2 and 3 were mixed in a double cone blender for 20 minutes to obtain a blend.

Step 4: Talc and Colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing Magnesium stearate for 5 minutes and was compressed to form tablets using 9mm Punch.

Example 2

S.No	Ingredients	%
1	Doxazosin Mesylate	3.56
2	Polyethylene glycol	5.45
3	Lactose	36.43
4	Methocel E-5	21.81
5	Methocel K-4MCR	14.54
6	Sodium alginate	3.636
7	Alginic Acid	5.45
8	Eudragit EPO	7.27
9	Mg. Stearate	0.727
10	Talc	0.727
11	Colloidal silicon dioxide	0.363

Process: -

Step 1: PEG melted on water bath and Doxazosin added to it and cooled with mixing. The cooled material is passed thru BSS # 44.

All other excipients were sifted through British Standard Sieve 44#. All the excipients were sifted through British Standard Sieve 44#.

Step 2: Methocel E-5, Methocel K-4MCR, Sodium alginate, Alginic acid, Eudragit EPO were mixed in Double cone blender for 20 minutes to obtain a blend.

Step 3: The granules of Polyethylene glycol & Doxazosin Mesylate & Lactose were mixed in double cone blender for 20 minutes to obtain a blend. Both the blends of step 2 and 3 were mixed in a double cone blender for 20 minutes to obtain a blend.

Step 4: Talc and Colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing Magnesium stearate for 5 minutes and was compressed to form tablets using 9mm Punch.

Example 3

S.No	Ingredients	%
1	Doxazosin Mesylate	3.01
2	Polyethylene glycol	7.69
3	Microcrystalline cellulose	35.38
4	Lactose	24.67
5	Methocel K100M CR	12.307
6	Methocel K100LV CR	15.38
7	Magnesium Stearate	0.615
8	Talc	0.615
9	Colloidal silicon dioxide	0.307

Process

Step 1: : PEG melted on water bath and Doxazosin added to it and cooled with mixing. The cooled material is passed thru BSS # 44.

All other excipients were sifted through British Standard Sieve 44#. All the excipients were sifted through British Standard Sieve 44#.

Step 2: Methocel K100MCR, Methocel K100LVCR & Lactose were mixed in double cone blender for 20 minutes to obtain a blend

Step 3: The granules of Polyethylene glycol & Doxazosin Mesylate & Microcrystalline cellulose were mixed in Double cone blender for 20 minutes to obtain a blend. Both the blends of step 2 and 3 were mixed in a double cone blender for 20 minutes to obtain a blend.

Step 4: Talc and Colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing Magnesium stearate for 5 minutes and was compressed to form tablets using 9mm Punch.

Example 4

S.No	Ingredients	%
	Intragnular	
1	Doxazosin Mesylate	3.21
2	Lactose	32.521
3	Methocel E-5	3.27
4	Citric acid *	16.39
	Extragranular	
5	Methocel E-5	16.39
6	Sodium alginate	3.27
7	Methocel K-4 MCR	11.47
8	Alginic acid	4.91
9	Eudragit EPO	6.55
10	Magnesium Stearate	0.983

11	Talc	0.65
12	Colloidal silicon dioxide	0.327

* PEG 6000 / Tartaric Acid / Lutrol F 407 / any other solubilizer / no solubilizer

Step 1: Doxazosin Mesylate was sifted through British Standard Sieve 22# and all other excipients were sifted through British Standard Sieve 44#

Step 2: Lactose, Methocel E-5 and Citric Acid (Tartaric acid, Malic acid, Fumaric acid, Maleic acid and / or any other solublizer) were mixed for 20 minutes to obtain a blend and the blend of step 2 was mixed with Doxazosin Mesylate for 15 minutes to obtain a blend.

Step 3 : Magnesium Stearate was added to the blend of step 3 with above blend and mixed for 5 minutes to obtain a blend

Step 4: Slugs were prepared of blend of step 3 and were broken and passed through British Standard Sieve 22# to obtain granules.

Step 5: Methocel E-5, Methocel K-4MCR, Keltone LVCR, Alginic Acid, Eudragit EPO were mixed to obtain a blend.

Step 6: Granules of Step 4 and blend of Step 5 were mixed for 20 minutes to obtain a blend.

Step 7: Talc and Colloidal silicon dioxide were mixed with blend of step 3 for 5 minutes followed by mixing Magnesium stearate for 5 minutes and was compressed to form tablets using 9mm Punch.

Example 5: Doxazosin 4 mg strength, if need to be included in the patent

S.N.	Ingredients	%
1	Doxazosin Mesylate	1.49
2	Polyethylene glycol	3.85
3	Microcrystalline cellulose	35.38
4	Lactose	24.7
5	Methocel K100M CR	14.68
6	Methocel K100LV CR	18.35
7	Magnesium Stearate	0.615
8	Talc	0.615
9	Colloidal silicon dioxide	0.307

The process of example 1 is followed to prepare the above formulation.

The optional coating with Opadry white or with following representative example may be used to coat doxazosin dosage form.

Ingredient	Percentage
Eudragit L 100 55:	22.4
NaOH:	0.3
PEG:	2.9
HPMC E 5:	67.2
Talc	6.7
Titanium dioxide:	0.5
Water	q.s.

Dated this 13TH day of **October, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

ORAL MATRIX FORMULATIONS OF DOXAZOSIN

The invention relates to the matrix formulation for extended release of doxazosin mesylate, comprising doxazosin or its salt, solvate, hydrates, enantiomer or mixtures thereof, at least one release retarding ingredient and other pharmaceutically acceptable excipient.